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From acute hypercalcaemia to post-parathyroidectomy hungry bone syndrome in a patient with primary hyperparathyroidism-associated brown tumours

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A 56-year-old female was admitted as an emergency for acute hypercalcaemia. Extremely high parathormone (PTH) with intact kidney function were consistent with primary hyperparathyroidism (PHP) (Tab. 1). She described bone pain and chronic asthenia for 2 years. She had arterial hypertension and entered menopause at 53. The family medical history was irrelevant. Imaging assessments pointed out a 4-cm inferior right parathyroid tumour (Fig. 1). No elements of multiple endocrine neoplasia were identified, nor kidney stones. After managing hypercalcemia through intravenous hydration and diuretics, a right inferior parathyroidectomy was performed (pathological exam: parathyroid adenoma of 3.4×3.2 cm, with principal cells, areas of haemorrhage and osteoid metaplasia, intact capsule, no atypia). She was early released with high-normal total calcium of 10.2 mg/dL and offered oral calcium (1 g/day) and vitamin D (alphacalcidol 1 μg/day and cholecalciferol 2000 UI/day). She was readmitted a few days later after experiencing diffuse bone pain, and paraesthesia which correlated with acute hypo-

Table 1. *Biochemistry and hormonal assays*

Parameter	Units	On admission	Second admission*	1-month check-up	Normal values	Units
Total serum Ca	mg/dL	14.76	**5.6 (6.9**)**	7.29	8.5–10.2	mg/dL
Total ionic Ca	mg/dL	5.63	2.82	3	3.9–4.9	mg/dL
Serum P	mg/dL	2.3	4	3.18	2.5–4.5	mg/dL
Serum Mg	mg/dL	1.9	1.6	1.9	1.6–2.4	mg/dL
PTH	pg/mL	1109	**70**	71	15–65	pg/mL
25OHD	ng/mL	11	12.8	15.9	30–100	ng/mL
24-h Ca	ng/mL	0.9	NA	0.01	0.07–0.3	ng/mL
AP	U/L	660	**492**	309	38–105	U/L
Osteocalcin	ng/dL	> 300	**> 300**	160	15–46	ng/dL
P1NP	ng/dL	NA	**408.8**	400	20.25–76.3	ng/dL
CrossLaps	ng/mL	5.07	**0.96**	1.4	0.33–0.782	ng/mL
Haemoglobin	g/dL	8.3 (9.3***)	7.3	6.7	12–15.5	g/dL

AP — total alkaline phosphatase; Ca — calcium; 24-h — 24-hour urinary calcium; Mg — magnesium; P — phosphorus; PTH — parathyroid hormone; 25OHD — 25-hydroxyvitamin D; NA — not available; blood bone turnover markers of formation (AP, osteocalcin, and P1NP) and of resorption (CrossLaps); blue — diagnosis HBS: symptomatic hypocalcaemia starting from the 4–5th post-operatory day and confirmed at lab assays, mild hypomagnesaemia, but normal phosphorus with high-normal PTH that excluded post-operatory hypoparathyroidism; probably with a mild component of hypovitaminosis D-related secondary hyperparathyroidism; *10 days since parathyroidectomy;**the second value was achieved after a 10-day hospitalization; ***after 2 U of red blood cells mass transfusion before surgery

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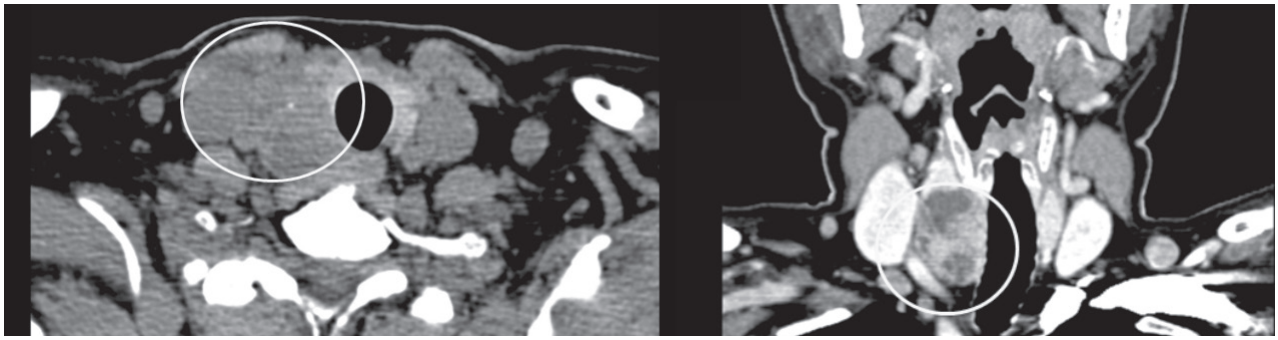

Figure 1. *CT: right later-cervical tumour of 2.4 × 4 cm (oval, well-shaped parathyroid mass; heterogeneous consistency, next to the right thyroid lobe, with mass effect on the right jugular vein and carotid artery. Transversal plan (left). Coronal plan (right)*

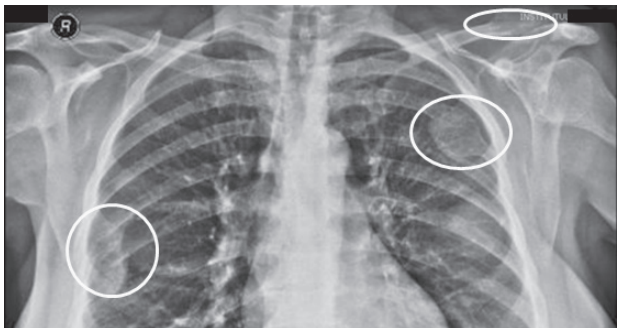

Figure 2. *Thorax X-Ray: brown tumours at the level of 2nd and 3rd left ribs (1.8 cm), 4th, 5th, and 6th right ribs (4 cm) and 1/3 external left clavicle (3 cm)*

calcaemia and hungry bone syndrome (HBS). Intensive intravenous calcium replacements (2–4 g/day) and oral calcitriol (1 g/day) were continued with cholecalciferol 2000 UI/day (total calcium increased from 5.6 to 6.9 mg/dL after a 10-day hospitalization). Due to bone complains an X-ray exam was done and confirmed by computed tomography (CT): 3 bone lesions at ribs and clavicle with cortical disruption (brown tumours) (Fig. 2). Osteoporosis was confirmed by DXA — lowest T score of –3.5. She was discharged with oral calcium and vitamin D replacements, with progressive clinical improvement as well as one-month blood assays, including previously high bone turnover markers. Monthly risendronate (75 mg × 2/month) was added. Long-term surveillance is needed; a resolution of brown tumours is expected.

Post-parathyroidectomy HBS is reported in 15–20% (if any) of cases with PHP; a higher risk is described in cases with elevated pre-operatory serum calcium, PTH (especially >1000 pg/mL) and alkaline phosphatase (mostly, 6 times upper normal limits), and, probably, low 25-hydroxyvitamin D, brown tumours, anaemia, large parathyroid tumours, and osteoid metaplasia (functional aspect of long-standing disease). Brown tumours, part of severe traditional bone complications in PHP, represent an exceptional event nowadays, being associated with longer disease duration, increased pre-surgery PTH, large parathyroid adenomas, and D hypovitaminosis. Their adequate recognition in relationship with a parathyroid condition avoids unnecessary bone biopsy, to exclude a malignancy, although a certain index of suspicion should be kept in mind and long-term surveillance is needed until their resolution. Remarkably, the patient presented severe hypochromic microcytic hyposideremic anaemia that required 2 units of red blood cells before surgery and long-term oral iron supplementation. A complete haematological exam was done, which found no other cause; no suspected malignancies, such as multiple myeloma that might mimic bone lesions, were confirmed. The potential mechanisms of anaemia in PHP are related to the following pathogenic traits: it represents an element of chronic illness, including calcium-induced loss of appetite and stomach pain, PTH-induced focal fibrosis of the marrow space, direct PTH inhibition of erythrocytes, increased peripheral calcium-mediated destruction of red cells, and (not in this case) chronic kidney failure either as a complication of a primary or renal hyperparathyroidism. Take-home message: exceptional presentations of PHP might be found; unusual complications and outcome make awareness mandatory even in the modern era, whereas the typical frame of the condition has shifted to a mild, rather asymptomatic disease with a good overall prognosis.

Ethics statement

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Data were collected retrospectively.

Author contributions

Conceptualization, methodology, writing, review and editing, and supervision: M.C. and C.N.

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Conflict of interest

The authors declare no conflict of interest.